JAPAN TOBACCO INC *JP 2003119137-A
2001.10.10 2001-313130(+2001JP-313130) *(2003.04.23)* A61K 31/382, 31/5513, 31/553, 31/554, A61P 31/18, C07D 243/14, 267/14, 281/08, 491/048, 495/04, 495/14, 513/14

HIV inhibitor acting on virus resistant to HIV transcriptase and protease, useful for increasing latent period before development of AIDS

C2004-004744

B(6-H, 14-A2B1, 14-L6) .3

NOVELTY

An HIV inhibitor contains a tricyclic compound comprising a fused benzene ring; a fused furan, pyrrole, benzene or dihydrobenzene ring; and a fused diazepine, thiazepine, oxazepine or dihydro thiapyran ring.

DETAILED DESCRIPTION

An HIV inhibitor contains a tricyclic compound of formula (I) or its salts.

Ring A = groups of formulae (A-a)-(A-d);

A^1 = 1-6C alkyl, 1-6C hydroxyalkyl, 2-6C alkenyl, phenylalkenyl, haloalkenyl, alkynyl, 2-11C acyl, 3-13C alkoxy carbonylalkyl, carboxyalkyl, or $-(CH_2)_n-r^{10}$;

A^8 = =N-O-r^{80}, =N-NH-r^{81} or =C-C(=O)-r^{82};

r^{80} = H, 1-6C alkyl, 2-11C acyl, 3-13C alkoxy carbonylalkyl or 2-7C carbamoyl alkyl;

r^{81} = 2-11C acyl or carbamoyl;

r^{82} = 1-6C alkoxy or amino;

R^1, R^2 = H, halo, 2-11C acyl, COOH, 2-7C alkoxy carbonyl, CN, NO_2, 5-tetrazolyl, -O-R^{10}, $-SO_2-N(R^{15})(R^{16})$, $-CO-N(R^{18})(R^{19})$, $-N(R^{20})(R^{21})$, -S-R^{22}, or $-SO_2-R^{25}$;

R^{10} = H, 1-6C alkyl, 2-6C alkenyl, $-SO_2-R^{11}$, $-(CH_2)_m-R^{14}$, 2-7C alkyl carbamoyl, di(1-6C alkyl)carbamoyl, 2-7C alkyl amino thiocarbonyl or di(1-6C alkyl)amino thiocarbonyl;

R^{11} = 1-6C alkyl, or groups of formulae (i)-(iv);

R^{12}, R^{13} = H, 1-6C alkyl or halo;

R^{14} = di(1-6C alkyl)amino, 1-6C alkoxy, 2-7C alkoxy carbonyl, CN, or the residue of 5 or 6 membered heterocycle which contains 1-4 nitrogen atoms;

m = 1-4;

R^{15}, R^{16} = H or 1-6C alkyl (optionally substituted by OH);

$NR^{15}R^{16}$ = piperazin-1-yl (optionally 4-substituted by 1-6C alkyl) or pyrrolidin-1-yl;

R^{17} = H or 1-6C alkyl;

R^{18}, R^{19} = H, 1-6C alkyl, or phenyl;

r^{10} = $-CO-N(r^{11})(r^{12})$, phenyl (optionally mono or di substituted, by 1-6C alkyl, 1-6C alkoxy, halo, NO_2, CN and/or 5-tetrazolyl) or pyridyl;

r^{11}, r^{12}, A^4, A^5, A^9, A^{10}, r^{70}, R^{23}, R^{24}, X^{20}, X^{21} = H or 1-6C alkyl;

$Nr^{11}r^{12}$ = piperazin-1-yl (optionally 4-substituted by 1-6C alkyl), pyrrolidin-1-yl, phenyl (substituted by r^{14} and r^{15}) or pyridinyl;

r^{14}, r^{15} = H, 1-6C alkyl, 1-6C alkoxy, halo, nitro, cyano, or tetrazol-5-yl;

n = 1-4;

A^2 = H, 1-6C alkyl, 2-6C alkenyl, benzyl, 2-11C acyl, acyloxy alkyl, 3-13 alkoxy carbonylalkyl, cyanoalkyl or di(1-6C alkyl)carbamoyl;

A^3 = -O, -S, or $-N(r^{30})-$;

r^{30} = H, 1-6C alkyl, or benzyl (optionally substituted by 1-6C alkyl, 1-6C alkoxy, halo or NO_2;

A^4-CH-CH-A^5 = cyclohexane ring;

A^6 = -S, -SO, or $-N(r^{60})$;

r^{60} = 1-6C alkyl or 2-6C alkenyl;

A^7 = -N=N-, -NH-CO-, $-CH_2-CH_2-$, -O-CO-, -O-CS-, $-N=C(r^{70})-$ or $-CH=C(r^{70})-$;

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R^{20}, R^{21} = H, 1-6C alkyl, 2-11C acyl, 1-6C alkyl sulfonyl, 2-7C alkoxy carbonyl, or alkenyl carbamoyl;

$NR^{20}R^{21}$ = piperidin-1-yl, maleimide, pyrrol-1-yl, 1,3,4-triazol-1-yl, or a group of formula (v);

R^{22} = 1-6C alkyl or $-CO-N(R^{23})(R^{24})$;

R^{25} = 1-6C alkoxy, 1-6C alkyl, 2-6C alkenyl, or benzyl;

X = S, O, $-CH_2-CH_2-$, -CH=CH-, or $-C(X^{20})(X^{21})-$; and

provided that, when Ring A is (A-a), A^1 is 1-6C alkyl and A^2 is H, then R^1 is not H, NO_2, halo, -O-R' or -N(R)(R') (where R', R and R' are each H or 1-6C alkyl).

ACTIVITY

Anti-HIV.

In tests on a clone of HL-60 cells incorporating the HIV-1 gene, (I: R^1 = OMe; A^1 = $-CH_2C(Me)=CH_2$; A^2 = Me; X = S) inhibited the increase of HIV-1 p24 antigen with MIC_{50} of below 80 nM.

MECHANISM OF ACTION

Inhibition of HIV-LTR under HIV-Tat stimulation (HIV-Tat transcription inhibitor).

In tests on cultures of 1A12 cell (The recombinant HeLa cells

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incorporating HIV-LTR promoter) treated with PCMV-Tat plasmid, (I: R^1 = OMe; A^1 = $-CH_2C(Me)=CH_2$; A^2 = Me; X = S), expression was inhibited with IC_{50} below 300 nM.

USE

In mammals, for increasing the latent period between acquiring HIV infection and developing AIDS, useful when virus has acquired resistance to reverse transcriptase or protease.

ADVANTAGE

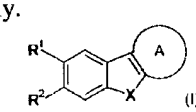
Suppresses HIV proliferation in virus with a different mechanism to antiretroviral (early stage) or protease inhibitor (late stage) drugs, and treatment with it can be given during and after highly active antiretroviral therapy (HAART).

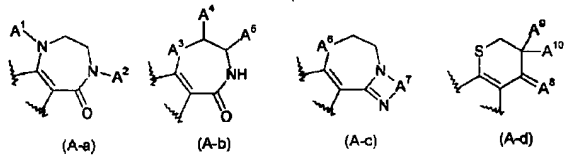
SPECIFIC COMPOUNDS

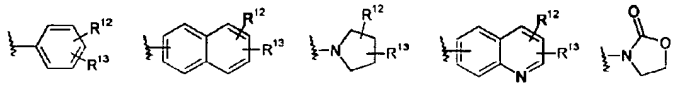
A disclosed compound of (I) is 3-methoxy-8-methyl-5-(2-methyl-allyl)-5,6,7,8-tetrahydro-10-thia-5,8-diaza-benzo[a]azulen-9-one (Ia).

ADMINISTRATION

1 to 1000 mg/kg body-weight once or more/day for an adult, e.g. orally.


(I)


(A-a) (A-b) (A-c) (A-d)


(i) (ii) (iii) (iv) (v)

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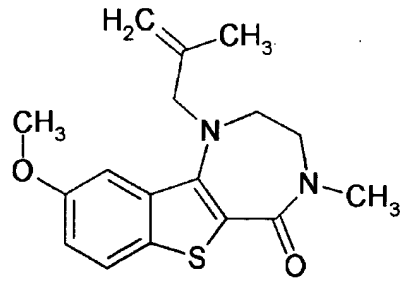

(Ia)

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